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Clinicopathological profile of neurotuberculosis in children in a tertiary care hospital of eastern india: A prospective observational study

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ABSTRACT

Introduction

Tuberculosis is common, especially in developing countries such as India. It is an important cause of morbidity and mortality in children. Neurotuberculosis is the most severe and life threatening form of disease in children.

Methods

This was a prospective observational study, designed with the objective to study neurotuberculosis in paediatric age group. Detailed history, examination and outcome were collected in a predesigned proforma from patients under 14 years of age admitted with neurotuberculosis from october 2014 to october 2016 in the pediatric ward of SVPPGIP, Cuttack, Odisha. 50 patients were included in the study. Data was analysed using Microsoft excel 2016, data was presented in the form of frequency and percentages.

Results

This study included 50 cases with male to female ratio of 1.4:1. The maximum incidence of neurotuberculosis was found in 6 months-3 years age group (58%). History of contact with known case was ascertained in 38% of cases, BCG scar was present in 62% of cases. The most common symptom was found to be fever (90% cases), followed by altered sensorium (70% cases), convulsion (64%). Mantoux test was found to be positive in 22% cases. Out of all cases 22% recovered completely, 30% cases died and 48% developed sequelae.

Conclusion

In children, clinical features remain inconclusive for diagnosing neurotuberculosis. Neurotuberculosis continues to be associated with high rate mortality in children of countries like India with high burden of TB.

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INTRODUCTION

Tuberculosis has re-emerged as a major public health challenge in the world. India has one of the highest tuberculosis (TB) burdens globally, accounting for 28% of the new 10.6 million TB cases in 2021.[1] In 2021, 82% of global TB deaths among HIV-negative people occurred in the WHO African and South-East Asia regions; India alone accounted for 36%. The African and South-East Asia regions accounted for 82% of the combined total of TB deaths in HIV-negative and HIV-positive people; India accounted for 32%. 24.2 lakhs TB cases were reported in India in 2022.[2]

Central nervous system (CNS) disease caused by *Mycobacterium tuberculosis* is an uncommon yet highly devastating manifestation of tuberculosis, which was universally fatal in the era before antituberculosis therapy. TB in children has a similar preponderance in girls and boys, especially younger children.[2] Globally, in 2021, children between 0-14 years of age constituted about 10.9% of the total estimated incident TB cases.[1] Children are rarely smear positive, approximately 95% of children of less than 12 years old with TB are smear negative. Hence, are much less likely to be a source of infection for others.[3] Infants and young children are at higher risk of developing life-threatening forms of TB disease (e.g., disseminated TB, TB meningitis) than older children and adults. Twenty-five percent of the pediatric tubercular cases are extrapulmonary, with tubercular meningitis (TBM) being the most common cause of death because of TB.[4] Around 10% of patients who have tuberculosis elsewhere in the body develop neurotuberculosis. Neurotuberculosis may be in the form of meningitis, intracranial tuberculoma or spinal tubercular arachnoiditis and rarely tuberculous encephalopathy. Tuberculous infection of CNS usually presents over weeks or months and because of insidious onset of symptoms, diagnosis may be delayed.[5]

MATERIALS AND METHODS

This was a prospective observational study, designed with the objective to study neurotuberculosis in paediatric age group, admitted in pediatric ward of SVPPGIP, Cuttack (Odisha) from October 2014 to October 2016. The diagnosis of TBM was based on the clinical case definition by modified Ahuja criteria (Text box 1).[3]

Text box 1: Modified Ahuja Criteria for diagnosis of TBM in children [3]

A. Mandatory features

- Fever lasting for more than 14 days
- Abnormal CSF findings (pleocytosis with more than 20 cells and more than 60% lymphocytes, protein >100 mg/dl, sugar <60% of corresponding blood sugar values)

In addition to the above, any 2 of the following features

- Evidence of extra neural tuberculosis
- Positive family history of exposure to a case of tuberculosis
- Positive mantoux reaction >10 mm
- Abnormal CT scan findings (2 or more of following): Exudate in the basal cistern or in the sylvian fissure, hydrocephalus, infarcts, gyral enhancement

Ethical clearance was obtained from the Institute Ethics Committee(IEC application number 102/dt 26.09.2014) and a written informed consent was taken from the parents before enrollment. TBM cases on treatment, children <6 months, cases whose parents were unwilling were excluded. On admission, a detailed history of the presenting complaints, the duration of illness, recent past history of measles, presence of household tuberculosis contact, vaccination status were obtained from the parents. Nutritional status of the children was assessed and socioeconomic status evaluated as per modified Kuppuswamy scale. Clinical examination for the level of consciousness, anthropometry, general and systemic examination findings, extent of neurological deficits was done. Staging of tubercular meningitis was done as per Medical Research Council Staging.[3] (Text box 2) Investigations such as CBC, ESR, LFT, Mantoux test, X-ray chest, gastric aspirate/sputum for AFB, CSF analysis (sugar, protein, cell count, ZN stain) were noted.. Data were collected in a predesigned proforma, checked for completeness and analysed in Microsoft excel 2016. Chi square test was used and data was presented in the form of frequency and percentage.

Text box 2: British Medical Research Council Staging of tuberculous meningitis (TBM) [3]
Stage I: The symptoms are nonspecific with few or no clinical signs of meningitis. The patient is fully conscious and alert Stage II: Signs of meningitis, drowsiness or lethargy, cranial nerve palsies Stage III: Severe clouding of consciousness, stupor or coma, convulsions, gross paresis or paralysis

RESULTS

In the present study, we got 182 cases of febrile encephalopathy, out of which 50 met the eligibility criteria and were included. Neurotuberculosis constituted 32%(n=50) of the total number of tuberculosis cases (n=154) admitted in our hospital. There was male preponderance (n=29, 58%) with male to female ratio of 1.4:1. (Table 1) The maximum incidence of NTB was found in lower age (6 months - 6 years) group i.e. 72%(n=36)and association between staging of TBM and age group was found to be statistically significant ($p < 0.05$)(calculated using chi-square test. 44% cases(n=22) were from the upper middle and upper lower socioeconomic class, 56%(n=28) from lower middle and lower socioeconomic class. 82%(n=41) children had mild to moderate malnutrition. History of contact with known case of tuberculosis was ascertained in 38%(n=19) of cases, most of which were their family members and 62%(n=31) subjects were vaccinated with BCG. (Table 1)

Table 1:Socio-demographic profile of study subjects

Variables	Stage II	Stage III	Total	P value
Age				
6 mo - < 6 years	24 (88.9%)	12 (52.2%)	36 (72%)	0.003
6 - 14 years	03 (11.1%)	11 (47.8%)	14 (28%)	
Gender				
Male	16 (59.3%)	13 (56.5%)	29 (58%)	0.845
Female	11 (40.7%)	10 (43.5%)	21 (42%)	
SES				
Upper middle/upper lower	11 (40.7%)	11 (47.8%)	22 (44%)	0.614
Lower middle /lower	16 (59.3%)	12 (52.2%)	28 (56%)	
Nutritional status				
I/II	21 (77.8%)	20 (86.9%)	41 (82%)	0.399
III	06 (22.2%)	03 (13.1%)	09 (18%)	
H/O Contact				
H/O Contact Present	13 (43.3%)	06 (30%)	19 (38%)	0.341
Vaccinated with BCG	17 (56.7%)	14 (70%)	31 (62%)	

When inquired about the symptoms, most common symptoms were fever (90% cases, n=45), followed by altered sensorium (70% cases, n=35) and convulsion (64%,n=32). (Table 2) Majority of the cases (54%, n=27) presented with TBM stage 2 and 46%(n=23) in TBM stage 3. There were no patients with stage 1 TBM.

Table 2: Clinical symptoms in study subjects

Presenting symptoms	Number of cases	Percentage (%)
Fever	45	90
Altered sensorium	35	70
Convulsion	32	64
Abnormal posturing	15	30
Headache	13	26
Irritability	13	26
Vomiting	12	24
Cough	7	14
Weakness of limbs	7	14
Refusal to feed	6	12
Weight loss	3	6
Paucity of movements	2	4
Increasing head size	1	2

On investigation, ESR was high in 28%(n=14) cases. (Table 3) LFT was within the normal range in all subjects. In this study, chest x-ray infiltrates was seen in 36%(n=18) cases. Mantoux test was positive in 22%(n=11) cases and 10%(n=5) tested positive for HIV. Out of 50 cases, 45 (90%) patients showed CSF pleocytosis. Forty-three (86%) showed total cell count in the CSF between 10 and 400 cells/mm^3. 33 (66%) patients had CSF lymphocytosis of over 80%, and 11 (22%) patients had CSF lymphocytosis of 20-80%. CSF glucose levels less than 60 mg/dL were seen in 90% (n=45) of cases. The CSF was acellular in five patients, although all of them had low glucose, elevated protein, or both in the CSF. Both CSF and gastric aspirate tested negative for AFB in all subjects. Out of all cases 22% (n=11) recovered completely, 30% (n=15) cases died and 48% (n=24) developed sequelae. (Table 3)

Table 3:Investigations/ outcome of study subjects

Investigations	No.	Percentage
CSF protein (mg/dL)		
<40	2	4%
40-100	14	28%
≥100	34	68%
CSF glucose (mg/dL)		
<40	20	40%
40-60	25	50%
≥60	5	10%
CSF total cells (n/mm^3)		
<10	5	10%

10-100	28	56%
100-400	15	30%
≥400	2	4%
CSF Lymphocyte percentage		
<20	6	12%
20-80	11	22%
>80	33	66%
Abnormality in chest X ray	18	36%
ESR>20mm/1st hr	14	28%
Mantoux positive	11	22%
HIV positive	5	10%
Outcome		
Improved	11	22%
Sequelae	24	48%
Death	15	30%

DISCUSSION

Neurotuberculosis is a form of tuberculosis where the infection affects the meninges, brain parenchyma or spinal cord. Meningitis is undoubtedly the most serious manifestation of tuberculosis. In this study, 72% (36) patients were under 5 years of age which is consistent with other studies, [5, 7, 14] globally children <5 years of age have been found to be most vulnerable. [12, 13] Male outnumbered females with the male: female ratio of 1.4:1. Neurotuberculosis constituted 32% of the total number of tuberculosis patients admitted in our hospital. 62% cases developed neurotuberculosis despite receiving BCG vaccination at birth. Several studies have shown that BCG protects against TBM and that its efficacy is around 75 to 85%. As per the study by Van Den Bos, [11] BCG is more effective in preventing neurological sequelae in neurotuberculosis patients than preventing the disease itself. Contact with cases of TB could be elicited in about 38 % of children in present study, this figure has been reported between 33% and 69% in various studies. [8, 12, 13] It emphasizes the importance of eliciting contact history in suspected cases of TBM. Fever was the most common symptom (90%) followed by altered sensorium (70%) and seizures (64%). Similar findings were observed in other studies. [5, 14] Altered sensorium varied from mild confusion to coma. Most of these patients developed altered consciousness after the onset of seizure. The causes of altered sensorium in tubercular meningitis include variable degrees of encephalitis, hydrocephalus, and infarction. [15] Most of the children (54%) in this study were detected in Stage II, rest in stage III. None of the patients were in stage I, which may be due to delay in seeking treatment and late referral. All the patients admitted with stage III died. Advanced stage is the single most important factor associated with poor outcome, [12] and the same has been echoed in our study.

A negative tuberculin test (Mantoux test) was seen in 39 cases (78%) which reflect the absence of immune-mediated hypersensitivity reaction to tuberculin, since neurotuberculosis commonly occurs with immunosuppression. Infiltrates in chest x- ray was found in 36% cases, the figure was 55% in another study. [16]

45 cases (90%) showed CSF pleocytosis, predominantly lymphocytic. CSF protein levels over 100 mg/dL were seen in 68% of patients. CSF glucose levels less than 60 mg/dL were seen in

90% of cases. This aligns with other studies[4, 14, 18]. The overall mortality in the present study was 30%, a previous systematic review reported this figure as 19.3%.[17] Neurological sequelae was observed in 48% cases on follow-up. Among the different sequelae, blindness (24%), learning disability (22%), motor deficit (20%), hydrocephalus (20%), mental retardation (20%) and behavioural disorder (18%) were common. Cranial nerve palsy (14%) and deafness (6%) were other complications observed. Sequelae were most commonly seen with stage II TBM. The strength of the present study are prospective enlistment of children for the study and documentation using a predesigned data collection form. The limitations are: small sample size, referral bias cannot be ruled out as it was a single centre study at a tertiary care, TB culture and nucleic acid amplification tests (GeneXpert) were not conducted on the CSF specimen.

CONCLUSION

In children, clinical features remain inconclusive for diagnosing neurotuberculosis.

Neurotuberculosis continues to be associated with high rate mortality in children of countries like India with high burden of TB. Even with the advancement of scientific knowledge and technologies very little prediction can be made regarding the prognosis of children. Hence, a high level of suspicion for neurotuberculosis in children must be maintained to prevent neurological morbidity, disability, and mortality.

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REFERENCES

1. Global tuberculosis report 2021 (pp15). Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240037021).
2. India TB report 2022 https://tbcindia.gov.in/showfile.php?lid=3680
3. Erwin Cooreman. Global epidemiology of pediatric tuberculosis: Introduction: Essentials of Tuberculosis in Children. ed. Vimlesh Seth, SK Kabra. 2006; 2:pp. 11-13.
4. Israni AV, Dave DA, Mandal A, Singh A, Sahi PK, Das RR, et al. Tubercular meningitis in children: clinical, pathological, and radiological profile and factors associated with mortality. *J Neurosci Rural Pract.* 2016;7:400–4.
5. Ramdas Dahiphale. Epidemiological pattern of neurotuberculosis in children. MedPulse International Journal of Pediatrics. May 2020; 14(2): 08-14.
6. Garcia-Monco JC. Central nervous system tuberculosis. Neurol Clin 1999;17:737-59.
7. Singh R, Shetty N, Naveed M, Talari MP, Verma D, Kulkarni V. Clinical profile of pediatric neurotuberculosis patients at a tertiary care center of Western India. Muller J Med Sci Res 2018;9:12-5.
8. Thilothammal N, Krishnamurthy PV, Banu K, Ratnam SR. Tuberculous meningitis in children – Clinical profile, mortality and morbidity of bacteriologically confirmed cases. *Indian Pediatr.* 1995;32:641–7. [PubMed] [Google Scholar]
9. Ramzan A, Nayil K, Asimi R, Wani A, Makhdoomi R, Jain A. Childhood tubercular meningitis: An institutional experience and analysis of predictors of outcome. *Pediatr Neurol.* 2013;48:30–5. [PubMed] [Google Scholar]
10. Central Nervous System Tuberculosis: Pathogenesis and Clinical Aspects R. Bryan Rock,* Michael Olin, Cristina A. Baker, Thomas W. Molitor, and Phillip K. Peterson
11. van den Bos F, Terken M, Ypma L, Kimpen JL, Nel ED, Schaaf HS, et al. Tuberculous meningitis and miliary tuberculosis in young children. *Trop Med Int Health.* 2004;9:309–13. [PubMed] [Google Scholar]
12. van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, et al. Twenty years of pediatric tuberculous meningitis: A retrospective cohort study in the western cape of South Africa. *Pediatrics.* 2009;123:e1–8.
13. Lee LV. Neurotuberculosis among Filipino children: An 11 years experience at the Philippine Children's Medical Center. *Brain Dev.* 2000;22:469–74. [PubMed] [Google Scholar] [Ref list]
14. Sharma V, Rajeshwari K, Kumar D, Gupta G. Clinicoepidemiological Profile and Prognostic Factors in Neurotuberculosis in Children. Ann Child Neurol. 2023;31(2):103-112.
15. Misra U.K., Kalita J., Roy A.K., Mandal S.K., Srivastava M.Role of clinical, radiological and neurophysiological changes in predicting the outcome of tuberculous meningitis: A multivariate analysis.*J Neurol Neurosurg Psychiatry.* 2000; 68: 300-303
16. Solomons RS, Goussard P, Visser DH, Marais BJ, Gie RP, Schoeman JF, van Furth AM. Chest radiograph findings in children with tuberculous meningitis. Int J Tuberc Lung Dis. 2015 Feb;19(2):200-4. doi: 10.5588/ijtld.14.0634. PMID: 25574919.
17. Graham SM, Donald PR. Death and disability: The outcomes of tuberculous meningitis. *Lancet Infect Dis.* 2014;14:902–4. [PubMed] [Google Scholar] [Ref list]
18. Gupta R, Kushwaha S, Thakur R, Jalan N, Rawat P, Gupta P, et al. Predictors of adverse outcome in patients of tuberculous meningitis in a multi-centric study from India. Indian J Tuberc 2017;64:296-301.